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REMARKS

Applicant thanks the Examiner for the courtesies extended to Applicant and its representatives during an interview on September 3, 2003. Amendments to the claims have been made following the Examiner's suggestions provided during the interview. A declaration showing the unexpected and surprising results achieved with the present invention are also submitted herewith as suggested by the Examiner.

Dr. Kline, the Applicant, provides a declaration attesting to the fact that others of skill in the art did not expect the amazing results achieved by using the present invention. This declaration provides brief descriptions of several patients treated according to the presently claimed invention. The declaration demonstrates that the presently claimed invention is capable of curing or managing cancer in those patients that are the most difficult to treat: patients that have not responded to traditional cancer therapies and whose cancer has or will progress so significantly that they are given only months to live. The declaration further indicates that it would not have been obvious to combine the prior art references listed below to arrive at the present invention. The incredible results obtained using the present invention and the declaration by Dr. Kline demonstrate that the present invention is not anticipated or obvious over the prior art.

After entry of this amendment, Claims 1-2, 4-9 and 13-17 are pending. Claims 12-15 have been renumbered to correctly reflect the existence of claims 10 and 11 cancelled previously. Claims 16 and 17 are added in effort to further define the invention. Support for Claim 16 can be found on at least page 5, lines 13-15 of the specification. No new matter has been added. Based on the following remarks, Applicant respectfully requests reconsideration and allowance of the pending claims.

Rejection of Claim 12 under 35 U.S.C. §112, first and second paragraph

The Examiner rejected Claim 12 as failing to comply with the written description requirement and as being indefinite. Applicant has cancelled Claim 12, and accordingly, the rejection is moot.

Rejection of Claims 1, 2, 4-9 and 12-15 under 35 U.S.C. §103(a)

The Examiner rejected Claims 1, 2, 4-9 and 12-15 under 35 U.S.C. § 103(a) as being unpatentable over Sedlacek *et al.*, Int. J. Immunopharmacol., 9 (7), 1987, abstract; Sedlacek, *et al.*, Cancer Immunol. Immunother. 23 (3), 1986, abstract; Maiskii *et al.*, Byull eksp biol med (12) 1977 (recd 1978) abstract [Maiskii 1978]; Knop *et al.*, Immunology, 34 (2), 1978 abstract; Gautam *et al.*, Indian J. Med. Res. 64 (3), 1976 abstract; Sedlacek, *et al.*, Cancer Immunology Immunother 1978 5/3 abstract; or Mobley *et al.*, Res. Commun. Chem. Path. Pharmacol. 1974, 9/1 abstract; taken with Green *et al.*, Kline *et al.*, '133 or Kline *et al.*, '863.

Applicant has obtained complete copies of the following articles: Sedlacek, *et al.*, Cancer Immunol. Immunother. 23:192-199, 1986 [Sedlacek 1986]; Sedlacek *et al.*, Int. J. Immunopharmac. 9(7):841-850, 1987 [Sedlacek 1987]; Knop *et al.*, Immunology, 34:181-187, 1978 [Knop 1978]; Gautam *et al.*, Indian J. Med. Res. 64 (3):472-481, 1976 [Gautam 1976]; Sedlacek, *et al.*, Cancer Immunol. Immunother. 5:153-163, 1978 [Sedlacek 1978]; Mobley *et al.*, Res. Commun. Chem. Path. Pharmacol. 9(1):155-162, 1974 [Mobley 1974] and Maiskii *et al.*, Byull eksp biol med (12) 1977 (translated and re-published in 1978) [Maiskii 1978]. Applicant thanks the Examiner for providing it with a complete copy of the Maiskii 1978 reference, however, Applicant is unable to determine the journal from which the Maiskii 1978 translation was obtained. Applicant requests that the Examiner provide such information. Applicant submits these articles herewith in a Supplemental Information Disclosure Statement.

The Examiner stated in a previous Office Action that the references each teach that an animal with a tumor was injected with neuraminidase, that Green provides the teaching of a phenol-saline carrier and that the Kline patents teach administration by sublingual and nasal routes. The Examiner further stated in the present Office Action that Sedlacek 1986 teaches the amount of enzyme that meets Applicant's claimed invention. Applicant traverses the rejection as follows.

None of the cited references teach a method of treating cancer by the administration of a small amount of neuraminidase, or approximately 10^{-2} mg to approximately 10^{-8} mg of neuraminidase. Each of the references either teaches nothing about cancer treatment in an individual, teaches co-administration of neuraminidase with a tumor cell, or teaches administration of neuraminidase alone in

unknown amounts or amounts much greater than the present invention. These teachings cannot be combined to arrive at the present invention. Accordingly, it is not obvious from the teachings of any of the references, either alone or in combination, that neuraminidase without a tumor cell and in small amounts could be used for the treatment of cancer.

Knop 1978 Cited Reference

The Knop 1978 reference does not teach or suggest the present invention because it contains no teaching or suggestion relating to cancer treatment in an individual. The scientific findings taught in the Knop 1978 reference are merely that co-administration of a red blood cell, a bacterial antigen or a viral antigen and neuraminidase to a mouse increases the mouse's immune response to the antigen. Accordingly, the scientific findings of the Knop 1978 reference only teach those of ordinary skill in the art that neuraminidase can act as an adjuvant, or in other words, that neuraminidase acts to increase the immunogenicity of the antigen with which it is administered. [Page 186, column 1, lines 1-2].

In an interview on September 3, 2003, the Examiner pointed out that the second sentence in the summary on page 181 refers to treatment of tumor cells with neuraminidase, and therefore, the Examiner submitted that this reference does teach treatment of a cancer with neuraminidase. Applicant respectfully disagrees with this interpretation. First, this sentence is found in a paragraph that summarizes the art prior to the 1978 Knop reference. The sentence does not give one of skill in the art any indication as to whether the tumor cells were treated while inside or outside an individual. Other statements in the introduction indicate that the authors of the article were in fact referring to treatment of tumor cells while they are outside the body of an individual. (See page 181, Column 2, lines 9-14). The present invention instead relates the treatment of a human having cancer. The sentence referred to by the Examiner also gives no indication as to the amount of neuraminidase used in the treatment. Accordingly, this sentence, the introduction, and the Knop 1978 reference as a whole provide no teachings or suggestions regarding administration of neuraminidase to a human in small amounts for the treatment of cancer. Therefore, the Knop 1978 reference does not teach or suggest the present invention.

Sedlacek 1986 and Sedlacek 1987 Cited References

Similar to the Knop 1978 reference, the Sedlacek 1986 and Sedlacek 1987 references describe the co-administration of neuraminidase with another molecule. These references teach that, in some cases, co-administration of both tumor cells and neuraminidase can be used for the treatment of cancer. The Sedlacek 1986 reference teaches that injection of both tumor cells and neuraminidase are required to achieve tumor regression. Page 196, column 2, line 6 through page 197, column 1, line 3 states: "The therapeutic effect in canine mammary tumors of chessboard vaccination was clearly dependent on the application of enzymatically active VCN [neuraminidase] and autologous tumor cells, as heat inactivated VCN mixed with autologous M-TC or autologous erythrocytes mixed with active VCN [neuraminidase] proved to be therapeutically inactive." Page 197, column 2, the second full paragraph further states: "Nevertheless, the studies in dogs show that a therapeutic effect of chessboard vaccination can only be achieved with autologous tumor cells and not with autologous erythrocytes." (Emphasis added in both quotations.) Accordingly, the Sedlacek 1986 reference teaches that a composition of neuraminidase and tumor cells is required for the treatment of cancer and that replacing the tumor cells with erythrocytes (red blood cells) causes the composition to become ineffective. The Sedlacek 1986 reference clearly teaches that tumor cells must be administered with neuraminidase for the treatment of cancer and therefore teaches away from the presently claimed composition that does not contain tumor cells.

The later Sedlacek 1987 reference also does not teach that neuraminidase alone can be administered to a human for the treatment of cancer. Instead, the Sedlacek 1987 reference teaches the administration of both tumor cells and neuraminidase. [Page 841, Abstract, lines 1-3.] The Sedlacek 1987 reference further teaches that administration of some types of tumor cells and neuraminidase combinations do not result in tumor regression [Page 846, lines 13-18].

Upon reading both the Sedlacek 1986 and 1987 references, one of ordinary skill in the art would understand that treatment of an animal with a tumor with both tumor cells and neuraminidase can be achieved in some cases, but not others. The Sedlacek references themselves teach that the tumor cell is an essential, non-omittable part of the Sedlacek et al. compositions. When Sedlacek omitted the tumor cell from

the neuraminidase composition, the result was no therapeutic effect. Accordingly, the 1986 or 1987 Sedlacek references teach away from the administration of neuraminidase without a tumor cell for cancer treatment.

The present invention does not require co-administration of a tumor cell and neuraminidase for the treatment of cancer as taught in the Sedlacek 1986 and Sedlacek 1987 references. The surprising finding of the present invention is that low amounts of neuraminidase can be administered without co-administration of a tumor cell for the treatment of cancer. As shown in the attached declaration by Dr. Kline, the amazing results achieved with the present invention were not expected by those of skill in the art. None of the Sedlacek 1986, Sedlacek 1987 and Knop 1978 cited references teach or suggest administration of neuraminidase without a tumor cell for the treatment of cancer. Accordingly, none of these references, either alone or in combination, render the present invention obvious.

Sedlacek 1978, Mobley 1974, Maiskii 1978 and Guatam 1976 Cited References

In contrast to the Sedlacek 1986 and Sedlacek 1987 references, each of the Sedlacek 1978, Mobley 1974, Maiskii 1978 and Guatam 1976 references teaches that neuraminidase alone can be injected into or near tumors or tumor challenge sites. Importantly however, each of this second set of references does not teach the amount of neuraminidase used or, in the alternative, requires the use of very high amounts of neuraminidase. The surprising finding of the present invention is that low amounts of neuraminidase can be administered without co-administration of a tumor cell for the treatment of cancer. As shown in the attached declaration by Dr. Kline, the amazing results achieved with the present invention were not expected by those of skill in the art. Since none of the Sedlacek 1978, Mobley 1974, Maiskii 1978 and Guatam 1976 references teach or suggest the use of low amounts of neuraminidase, none of these references render the present invention obvious.

None of the Mobley 1974, Maiskii 1978 and Guatam 1976 references teach the amount of neuraminidase used by those researchers. Both Mobley and Maiskii teach the injection of 50 units of neuraminidase [Mobley 1974 at page 157 lines 11-12 and Maiskii 1978 at page 1756, Experimental Method, second paragraph] and Guatam teaches the injection of 100 units of neuraminidase [page 474, lines 10-12]. However, none of these references provide the specific activity of the neuraminidase

used. One of ordinary skill in the art can only speculate as to the actual gram amount of neuraminidase used in each of these references. Applicant respectfully submits that these references do not render the present invention obvious since they contain no specific teachings regarding the amount of neuraminidase to be used for cancer treatment.

Even if one of ordinary skill in the art did attempt to correlate the neuraminidase in the Mobley 1974, Maiskii 1978 and Guatam 1976 references to the neuraminidase currently sold by commercial manufacturers, such a broad range of neuraminidase amounts would be obtained that the references would still be uninstructive. For example, concentrations of one type of neuraminidase, neuraminidase from *Vibrio cholerae*, are currently provided in ranges from 8 to 24 units per mg (Sigma); 1 to 3 units per mg (Sigma); and 20 units per mg (Roche). One of ordinary skill in the art would therefore be required to experiment with a dose of neuraminidase anywhere between 2.08 mg (50 units at 24 units/mg) to 100 mg (100 units at 1 unit per mg). Applicant respectfully submits that such experimentation is undue, and therefore, the Mobley 1974, Maiskii 1978 and Guatam 1976 references do not provide sufficient teachings regarding the amount of neuraminidase to be used for the treatment of cancer and do not render the present invention obvious.

Applicant further submits that present invention falls outside the broad range of amounts of neuraminidase possibly taught in the Mobley 1974, Maiskii 1978 and Guatam 1976 references. In stark contrast to high amounts of neuraminidase potentially gleaned from the Mobley 1974, Maiskii 1978 and Guatam 1976 references, the present invention requires approximately 0.01 (10^{-2}) mg to approximately 0.00000001 (10^{-8}) mg of neuraminidase. The amounts of neuraminidase possibly suggested in the Mobley 1974, Maiskii 1978 and Guatam 1976 references (2.08 mg to 100 mg) are 1000 to 100 million times greater than Applicant's currently claimed methods. Accordingly, applying present day manufacturing practices to these almost 30 year old references results in a teaching away from the present invention.

Finally, the Sedlacek 1978 reference, a review of neuraminidase use, also teaches away from the present invention on page 156, column 2, lines 11-15 wherein it is stated that "intratumoral injection of low amounts of VCN had no effect on tumor growth..." (emphasis added).

Accordingly, none of the Sedlacek 1978, Mobley 1974, Maiskii 1978 and Guatam 1976 references teach or suggest administration of neuraminidase in amounts between approximately 0.01 (10^{-2}) mg to approximately 0.00000001 (10^{-8}) mg. Instead, each of these references either provides insufficient teachings regarding neuraminidase amounts used for the treatment of cancer or teaches away from Applicant's present invention. Any teaching of the Mobley 1974, Maiskii 1978 and Guatam 1976 references found to be sufficient leads one of ordinary skill in the art away from the present invention by requiring huge amounts of neuraminidase, amounts 1000 to 100 million times greater than the present invention. The Sedlacek 1978 reference specifically teaches away from the present invention by stating that using low amounts of neuraminidase is ineffectual for the treatment of cancer. Therefore, none of these references, either alone or in combination, render the present invention obvious.

Combination of all Cited References

The Examiner noted in the most recent Office Action that the Sedlacek 1986 reference teaches the use of 0.01 units of neuraminidase, and therefore teaches the amount of neuraminidase currently claimed by Applicant. However, it must be remembered that the Sedlacek 1986 reference requires the administration of both neuraminidase and tumor cells. In order for the Examiner's obviousness rejection to be proper, it must have been obvious for one of ordinary skill in the art to combine the Sedlacek 1986 reference with one or more of the second set of references teaching injection of neuraminidase alone and such combination must result in the present invention.

Applicant respectfully submits that it would not have been obvious to combine Sedlacek 1986 with any of the Sedlacek 1978, Mobley 1974, Maiskii 1978 and Guatam 1976 references because these references teach away from each other and from the present invention. The Sedlacek 1986 reference only teaches that co-administration of both tumor cells and neuraminidase can result in tumor regression. In fact, the Sedlacek 1986 reference teaches that removing the tumor cells and replacing them with erythrocytes (red blood cells) causes the composition to become ineffective. Accordingly, the Sedlacek 1986 reference teaches that the tumor cell cannot be removed from a neuraminidase composition containing low amounts of neuraminidase and still be effective for the treatment of cancer. Those cited

references that do teach administration of neuraminidase without a tumor cell (Mobley 1974, Maiskii 1978, Guatam 1976 and Sedlacek 1978), fail to provide enough guidance about the amount of neuraminidase used. Even if one of ordinary skill in the art were to engage in undue experimentation to determine the amount of neuraminidase taught by any one of the Mobley 1974, Maiskii 1978, Guatam 1976 references, that person would conclude those references teach the use 1000 to 100 million times greater amounts of neuraminidase than Applicant's present invention.

Taken together, one of ordinary skill in the art would understand the totality of the cited references to teach that lower amounts of neuraminidase can be used for the treatment of a cancer when a tumor cell is co-administered with the neuraminidase, but that huge increases in neuraminidase are required when the tumor cell is removed and only neuraminidase is administered. Despite these teachings, Applicant has found that neuraminidase can be administered in low amounts without tumor cells for the treatment of cancer. Applicant's methods are far superior to administration of neuraminidase with tumor cells since it is quite dangerous to inject an individual with any form of cancer. Applicant's methods are also far superior to administration of neuraminidase in high amounts since some studies have shown that high amounts of neuraminidase actually increase tumor size [Sedlacek 1978, page 156, column 2, lines 11-15].

The enormous advantages of the present invention over the prior art are further reflected in the opinions of those of skill in the art. Submitted herewith is a declaration by the Applicant, Dr. Ellis Kline. This declaration demonstrates the amazing ability of the present invention to cure terminally ill cancer patients. Although several Australian doctors were first skeptical of Applicant's present invention and its potential efficacy, these doctors agreed to treat several terminally ill cancer patients with the compositions of the present invention as a last resort. These patients had been treated with traditional cancer therapies with no success and many of them were given only months to live when they began receiving the treatments of the present invention. To the doctors' great surprise, many of these patients' cancer were in complete remission several months after initiating treatment. The declaration submitted herewith provides a description of several of these patient's treatment and demonstrates that the present invention does in fact treat cancer, that it works to treat multiple different cancers, and that it works in patients with very advanced stage

cancers that could not be treated with other available therapies. The declaration further indicates that the results achieved using the present invention were greatly unexpected and that it would not have been obvious to combine the prior art references cited by the Examiner to arrive at the present invention.

Accordingly, Applicant respectfully submits that the present invention is not obvious over the Sedlacek 1986, Sedlacek 1987, Knop 1978, Mobley 1974, Maiskii 1977, Guatam 1976 and/or Sedlacek 1978 references. Those of skill in the art had over ten years to contemplate the references cited in the Office Action and none other than the present Applicant arrived at the present invention. Applicant submits that none of the cited prior art references teach or suggest the present invention, and that they instead teach away from the present invention. One of ordinary skill in the art would understand the totality of the cited references to teach that lower amounts of neuraminidase can be used for the treatment of a cancer when a tumor cell is co-administered with the neuraminidase, but that huge increases in neuraminidase (1000 to 100 million time more) are required when the tumor cell is removed and only neuraminidase is administered. Despite these teachings, Applicant has found that neuraminidase can be administered in low amounts without tumor cells for the treatment of cancer.

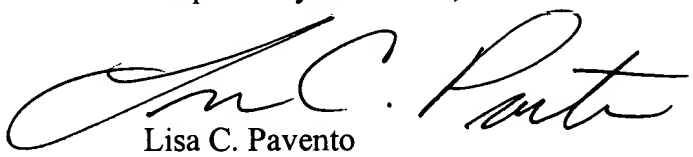
Applicant further submits that the Green *et al.*, Kline *et al.*, '133 and Kline *et al.*, '863 references add no additional teachings that would render the present invention obvious. As stated by the Examiner in an earlier telephone conference, Green "was cited as a general teaching to show the wide use of phenol-saline as a solution for injection of biological materials into the body", and as such, does not, in combination with the cited references, result in a teaching that renders the currently pending claims obvious. The same is true for the Kline patents, which were cited for teaching administration routes, and in combination with the other cited references, do not provide a teaching that renders the currently pending claims obvious.

For at least these reasons, Applicant respectfully submits that none of the cited references, either alone or in combination, render the present invention obvious. Applicant therefore requests the Examiner to withdraw the rejection.

CONCLUSION

The foregoing is a complete response to the Office Action mailed June 3, 2003. Applicant respectfully submits that the present application is in condition for immediate allowance. An early notification is earnestly solicited. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855. If the Examiner has any questions, or further issues remain to be resolved, the Examiner is requested to contact the undersigned at (404) 745-2517.

Respectfully submitted,



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